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(54) Novel quinolonecarboxylic acid derivatives.

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(73) Proprietor: **Chugai Seiyaku Kabushiki Kaisha**
5-1, 5-chome, Ukima
Kita-ku
Tokyo (JP)

(72) Inventor: **Nagano, Hiroyuki**
2-9-17, Ohta
Iwatsuki-shi
Saitama-ken (JP)
Inventor: **Yokota, Takeshi**
3-7-1, Narashinodai
Funabashi-shi
Chiba-ken (JP)
Inventor: **Katoh, Yasuyuki**
750-10, Tokura
Mishima-shi
Shizuoka-ken (JP)

(74) Representative: **VOSSIUS & PARTNER**
Postfach 86 07 67
D-81634 München (DE)

EP 0 342 675 B1

Description

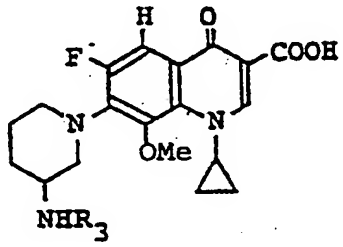
The present invention relates to novel quinolonecarboxylic acid derivatives that exhibit strong antibacterial activity and are useful as medicines.

A number of quinolone antibiotics are known, including commercially available ones, but they involve certain problems such as the fact that these compounds must be used with utmost caution because many of them show side-effects in the central nervous system. Recently, much attention has been paid to the antibacterial activity of quinoline derivatives that have a fluorine substituent at both 6- and 8-position, or a fluorine substituent at 6-position and a lower alkoxy substituent at 8-position (US-A-4 556 658, EP-A-106 489, EP-A-230 295, EP-A-241 206).

However, they are not always satisfactory antibiotics, since many of them have phototoxicity along with the side-effects mentioned above.

Thus, it is the object of the present invention to overcome the above drawbacks in the prior art.

This object has been achieved by the surprising finding that compounds of the general formula (1) shown below which have at 7-position a piperidin-1-yl group whose 3-position is substituted by an amino, which is optionally substituted by a lower alkyl having 1 to 3 carbon atoms, for example, the 3-aminopiperidin-1-yl group, exhibit higher antibacterial activity with fewer side-effects than known quinolone antibiotics such as ofloxacin and norfloxacin. Further, the compounds of the present invention having the general formula (1) have reduced phototoxicity which normally accompanies 6,8-difluoroquinoline antibiotics.



(I)

(wherein R_3 is a hydrogen atom or a lower alkyl having 1 to 3 carbon atoms.)

The quinolone derivatives of this invention having the general formula (1) are novel compounds. They may be prepared by the reaction of 3-acetamidopiperidines with known starting materials, for example, 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid, 5-amino-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid or a lower alkyl ester thereof followed by hydrolysis and the reaction of the compound obtained from the foregoing step with sodium methoxide. While there exist two optical isomers of each compound of the invention having the general formula (1), both of them can be utilized as compounds of the invention. In the case of synthesis of an optical active compound, for instance, starting with 3-aminopiperidine that has been prepared from optical active ornithine, the synthesis may be performed in a manner similar to that described above.

Preferable examples of the compound of the invention having the general formula (1) include 7-(3-aminopiperidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid and 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methylaminopiperidin-1-yl)-4-oxoquinoline-3-carboxylic acid.

The compounds of the invention form salts with acids. Examples of pharmaceutically acceptable acids include inorganic acids such as hydrochloric acid, sulfuric acid and nitric acid and organic acids such as oxalic acid, fumaric acid, and p-toluenesulfonic acid.

Reference Example 1.

(a) A mixture of ethyl 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (933 mg), 3-acetamidopiperidine (710 mg), triethylamine (400 mg) and dimethylsulfoxide (10 ml) was heated at 100°C for 2 hours with stirring. Thereafter the mixture was cooled down and ice water was added thereto. The resulting mixture was extracted with chloroform and the chloroform layer was washed with water three times before being dried over anhydrous sodium sulfate. Removal of the solvent in vacuum followed by purification by silica gel column chromatography (chloroform-ethanol) gave ethyl 7-(3-acetamidopiperidin-1-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (930 mg).

Recrystallization from ethanol-ether afforded a colorless crystalline substance (m.p. 217 - 218 °C).
(b) Ethyl 7-(3-acetamidopiperidin-1-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate obtained from the foregoing step (a) (433 mg) was dissolved in 6 N hydrochloric acid (5 ml) and heated at 100 °C for 2.5 hours with stirring. After the removal of the solvent in vacuum, methanol was added to the residue and the insoluble materials were filtered off. Removal of the solvent followed by purification by silica gel column chromatography (chloroform-methanol) gave hydrochloride of 7-(3-aminopiperidin-1-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (colorless, crystalline-powder), m.p.: color change at about 272 °C; decomposition at about 280 °C.

IR (KBr) ν cm^{-1}	1735, 3450
MS m/e	363 (M^+), 362

Example 1

(a) A mixture of 7-(3-acetamidopiperidin-1-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (4.05 g), sodium methoxide (2.16 g) and N,N-dimethylformamide (120 ml) was stirred for 2 hours at 100 - 140 °C. The reaction mixture was concentrated in vacuum and water was added to the residue. The mixture was neutralized with 1 N hydrochloric acid and the neutralized mixture was then concentrated in vacuum. Purification of the concentrated mixture by silica gel column chromatography (chloroform-methanol) gave 7-(3-acetamidopiperidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid. m.p. 248 - 250 °C.
(b) 7-(3-Acetamidopiperidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid (1.25 g) obtained from the foregoing step (a) was suspended in 6 N hydrochloric acid (30 ml) and ethanol (5 ml) and heated at 100 °C for 3 hours. Then the reaction mixture was concentrated in vacuum and the residue was purified by silica gel column chromatography (chloroform: methanol:ammonium hydroxide = 100:30:5) to afford 7-(3-aminopiperidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid. m.p. 176 - 177 °C.

Example 2

A mixture of 7-(3-aminopiperidin-1-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (1.21 g) obtained as described in Reference Example 1(b), sodium methoxide (1.2 g) and dimethylsulfoxide (40 ml) was stirred for 2 hours at 120 - 140 °C. The reaction mixture was concentrated in vacuum and water was added to the residue. Neutralization of the mixture with 1 N hydrochloric acid followed by evaporation of the solvent and purification by silica gel column chromatography (chloroform:methanol: ammonium hydroxide = 100:30:5) gave 7-(3-aminopiperidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid. The physical properties of this product were identical with those of the compound obtained in Example 1.

Example 3

To a suspension of 7-(3-aminopiperidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid obtained as described in Example 1 or 2 in a mixture of chloroform and methanol (1:1) was added dropwise methanolic hydrochloric acid and the mixture was worked up in a conventional manner to give hydrochloride of 7-(3-aminopiperidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid. m.p. 188 - 190 °C (decomposition).

Example 4

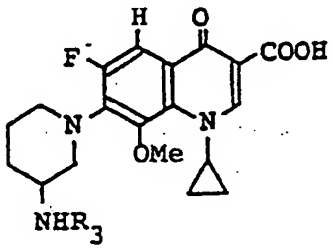
A mixture of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid (2.95 g), 3-methylaminopiperidine dihydrochloride (6.69 g) and triethylamine (10 g) in acetonitrile (50 ml) was refluxed with stirring for 12 hours. The reaction mixture was concentrated in vacuum, and the residue was extracted with chloroform. The extract was washed with a saturated NaCl solution and concentrated in vacuo. The residue was purified by silica gel column chromatography (chloroform: methanol:ammonium hydroxide = 15:5:1) to give 1.28 g of 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methylaminopiperidin-1-yl)-4-oxoquinoline-3-carboxylic acid, which was recrystallized from acetonitrile-wa-

ter, colorless needles. m.p. 134 - 135 °C.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Compounds illustrated by the general formula (I)



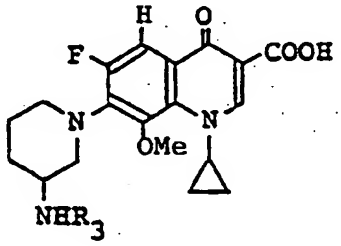
(I)

wherein R_3 is a hydrogen atom or a lower alkyl having 1 to 3 carbon atoms, and salts thereof.

2. 7-(3-Aminopiperidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid.

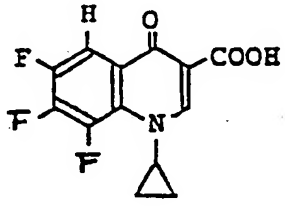
3. 1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methylaminopiperidin-1-yl)-4-oxoquinoline-3-carboxylic acid.

4. A method for producing compounds illustrated by the general formula (I)



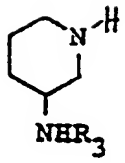
(I)

wherein R_3 is a hydrogen atom or a lower alkyl having 1 to 3 carbon atoms, and salts thereof, which comprises
reacting a compound illustrated by the general formula (II)



(II)

with a compound illustrated by the general formula (III)



(III)

wherein R_3 is defined as above, if appropriate in the presence of an acid-binding agent, and reacting the compound obtained with sodium methoxide.

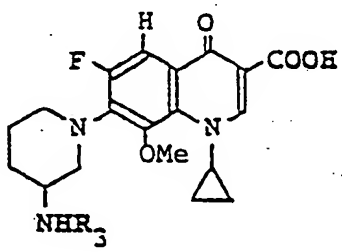
5. A pharmaceutical composition, comprising a compound of the general formula (I) according to any one of claims 1 to 3 and a carrier.

6. A compound of the general formula (I) according to any one of claims 1 to 3 for use in a method of treating bacterial infections.

7. The use of a compound of the general formula (I) according to any one of claims 1 to 3 for the preparation of a pharmaceutical composition for treating bacterial infections.

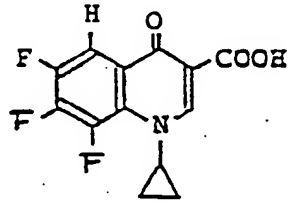
Claims for the following Contracting State : ES

1. A method for producing compounds illustrated by the general formula (I)



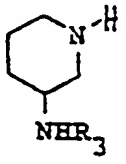
(I)

wherein R_3 is a hydrogen atom or a lower alkyl having 1 to 3 carbon atoms, and salts thereof, which comprises
reacting a compound illustrated by the general formula (II)



(II)

with a compound illustrated by the general formula (III)



(III)

wherein R_3 is defined as above, if appropriate in the presence of an acid-binding agent, and

reacting the compound obtained with sodium methoxide.

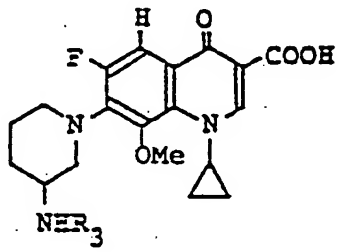
2. The method of claim 1 for the production of 7-(3-Aminopiperidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid.

3. The method of claim 1 for the production of 1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methylaminopiperidin-1-yl)-4-oxoquinoline-3-carboxylic acid.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Verbindungen der allgemeinen Formel (I)



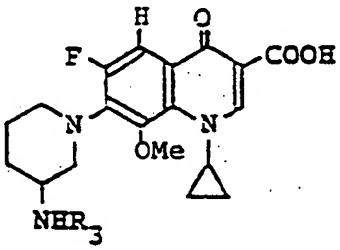
(I)

in der R_3 ein Wasserstoffatom oder ein Niederalkylrest mit 1 bis 3 Kohlenstoffatomen ist, und Salze davon.

2. 7-(3-Aminopiperidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxochinolin-3-carbonsäure.

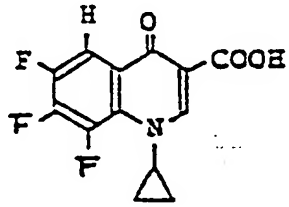
3. 1-Cyclopropyl-6-fluor-1,4-dihydro-8-methoxy-7-(3-methylaminopiperidin-1-yl)-4-oxochinolin-3-carbonsäure.

4. Verfahren zur Herstellung von Verbindungen der allgemeinen Formel (I)



(I)

in der R_3 ein Wasserstoffatom oder ein Niederalkylrest mit 1 bis 3 Kohlenstoffatomen ist, und Salzen davon, umfassend die Umsetzung einer Verbindung der allgemeinen Formel (II)



(II)

mit einer Verbindung der allgemeinen Formel (III)

(III)

wobei R_3 die vorstehend angegebene Bedeutung hat, falls geeignet in Gegenwart eines säurebindenden Mittels und Umsetzung der erhaltenen Verbindung mit Natriummethanolat.

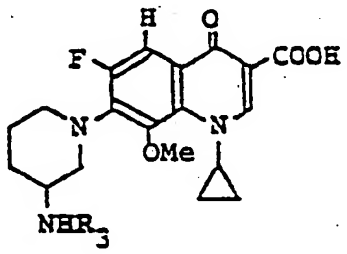
5. Arzneimittel, umfassend eine Verbindung der allgemeinen Formel (I) nach einem der Ansprüche 1 bis 3 und einen Träger.

6. Verbindung der allgemeinen Formel (I) nach einem der Ansprüche 1 bis 3 zur Anwendung bei einem Verfahren zur Behandlung von bakteriellen Infektionen.

7. Verwendung einer Verbindung der allgemeinen Formel (I) nach einem der Ansprüche 1 bis 3 zur Herstellung eines Arzneimittels zur Behandlung von bakteriellen Infektionen.

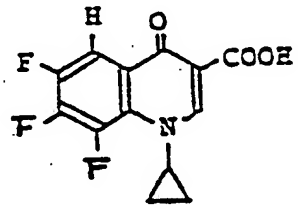
Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung von Verbindungen der allgemeinen Formel (I)



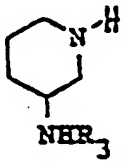
(I)

in der R_3 ein Wasserstoffatom oder ein Niederalkylrest mit 1 bis 3 Kohlenstoffatomen ist, und Salzen davon, umfassend die Umsetzung einer Verbindung der allgemeinen Formel (II)



(II)

mit einer Verbindung der allgemeinen Formel (III)



(III)

wobei R_3 die vorstehend angegebene Bedeutung hat, falls geeignet in Gegenwart eines säurebinden-

den Mittels und Umsetzung der erhaltenen Verbindung mit Natriummethanolat.

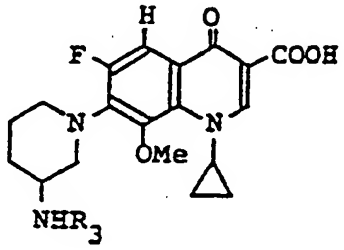
2. Verfahren nach Anspruch 1 zur Herstellung von 7-(3-Aminopiperidin-1-yl)-1-cyclopropyl-6-fluor-1,4-dihydro-8-methoxy-4-oxochinolin-3-carbonsäure.

3. Verfahren nach Anspruch 1 zur Herstellung von 1-Cyclopropyl-6-fluor-1,4-dihydro-8-methoxy-7-(3-methylaminopiperidin-1-yl)-4-oxochinolin-3-carbonsäure.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, NL, SE

1. Composés représentés par la formule générale (I)



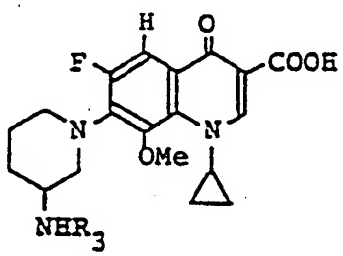
(I)

dans laquelle R_3 est un atome d'hydrogène ou un groupe alkyle inférieur comportant 1 à 3 atomes de carbone, et leurs sels.

2. Acide 7-(3-aminopipéridine-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-méthoxy-4-oxoquinoléine-3-carboxylique.

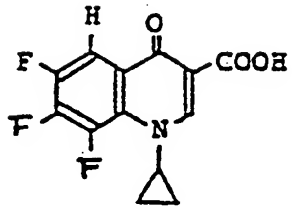
3. Acide 1-cyclopropyl-6-fluoro-1,4-dihydro-8-méthoxy-7-(3-méthylaminopipéridine-1-yl)-4-oxoquinoléine-3-carboxylique.

4. Procédé de production de composés représentés par la formule générale (I)



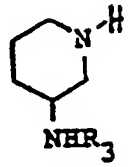
(I)

dans laquelle R_3 est un atome d'hydrogène ou un groupe alkyle inférieur comportant 1 à 3 atomes de carbone, et de leurs sels,
qui comprend la réaction d'un composé représenté par la formule générale (II)



(II)

avec un composé représenté par la formule générale (III)



(III)

dans laquelle R_3 est tel que défini ci-dessus, éventuellement en présence d'un agent de liaison à un acide, et la réaction du composé obtenu avec du méthylate de sodium.

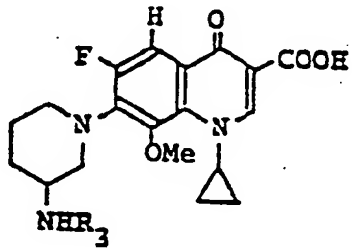
5. Composition pharmaceutique comprenant un composé de formule générale (I) selon l'une quelconque des revendications 1 à 3 et un véhicule.

6. Composé de formule générale (I) selon l'une quelconque des revendications 1 à 3 à utiliser dans un procédé de traitement d'infections bactériennes.

7. Utilisation d'un composé de formule générale (I) selon l'une quelconque des revendications 1 à 3 pour la préparation d'une composition pharmaceutique pour le traitement d'infections bactériennes.

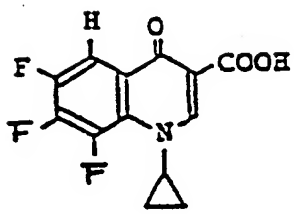
Revendications pour l'Etat contractant suivant : ES

1. Procédé de production de composés représentés par la formule générale (I)



(I)

dans laquelle R_3 est un atome d'hydrogène ou un groupe alkyle inférieur comportant 1 à 3 atomes de carbone, et de leurs sels,
qui comprend
la réaction d'un composé représenté par la formule générale (II)



(II)

avec un composé représenté par la formule générale (III)

(III)

dans laquelle R_3 est tel que défini ci-dessus, éventuellement en présence d'un agent de liaison à un acide, et la réaction du composé obtenu avec du méthylate de sodium.

2. Procédé selon la revendication 1, pour la production de l'acide 7-(3-aminopipéridine-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-méthoxy-4-oxoquinoléine-3-carboxylique.

3. Procédé selon la revendication 1, pour la production de l'acide 1-cyclopropyl-6-fluoro-1,4-dihydro-8-méthoxy-7-(3-méthylaminopipéridine-1-yl)-4-oxoquinoléine-3-carboxylique.